NIR as a PAT tool for solid and liquid forms manufacturing – Development and validation of in-line quantitative methods

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Purpose: First, to interface with NIR spectroscopy a particle and liquid flow typically observed in the manufacturing line. Secondly, based on those interfacings, to build NIR models able to quantify the active content of the two formulations. Finally, to validate the methods for an active content ranging from 80 to 120 % of the targeted active content. Finally, the applicability of such methods was discussed.

Methods: The particle flow was non-invasively interfaced with the reflectance module of a FT-NIR spectrometer whereas a transmittance probe was used to analyze the liquid form. Spectra of samples with 3 different API contents were collected. The quality of spectral acquisitions was then evaluated by PCA. For quantitative purpose, variability sources such as production campaigns, batches and days were introduced in the calibration and validation sets. PLS regression on the calibration set was performed to build prediction models of which the ability to quantify accurately was tested with the validation set.

Results: The quality of spectral acquisition for both liquid and solid forms was indicated by the PCA results which highlighted a clustering given the active content of the samples. The values of conventional criteria such as RMSEC, RMSECV and RMSEP suggested the prediction models overall good accuracy. Further, a novel approach based on tolerance intervals and ICH Q8R1 compliant, the accuracy profile on the validation results, enabled to visualize and demonstrated the adequate accuracy of the NIR methods over the chosen active content range. Finally, the NIR method for liquids was successfully used to prevent out of specifications products.

Conclusion: Typical solid and liquid flows were successfully interfaced with NIR spectroscopy. The developed interfacings allowed the development and the validation of quantitative methods able to determine the active content of those formulations. The accuracy profile on the validation results gave a complete accuracy report of the NIR methods and demonstrated their fit for purpose. It guarantees that the newly developed NIR methods will properly evaluate if the products comply with the active content specifications. Accordingly, those NIR methods pave the way for a real time release quality system-based.